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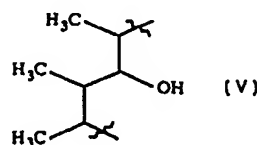
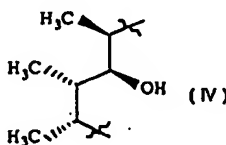
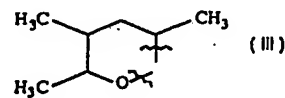
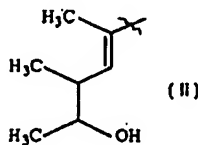
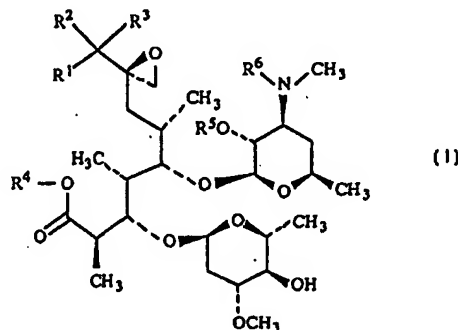
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(21) International Application Number: PCT/HR99/00035 (22) International Filing Date: 29 December 1999 (29.12.99) (30) Priority Data: P980646A 30 December 1998 (30.12.98) HR (71) Applicant (for all designated States except US): PLIVA, FAR- MACEUTSKA INDUSTRIJA. DIONIČKO DRUŠTVO [HR/HR]; Ulica grada Vukovara 49, 10000 Zagreb (HR). (72) Inventors; and (75) Inventors/Applicants (for US only): BUREK, Gordana [HR/HR]; Labinska 8, 10000 Zagreb (HR). LAZAREVSKI, Gorjana [HR/HR]; Barutanski jarak 18, 10000 Zagreb (HR). KOBREHEL, Gabrijela [HR/HR]; Trg Ivana Kukuljevića 3, 10000 Zagreb (HR). (74) Common Representative: PLIVA D.D.; Pravni Poslovi, Vesna Vasiljevic, Ulica grada Vukovara 49, 10000 Zagreb (HR).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL DERIVATIVES FROM THE CLASS OF OLEANDOMYCIN

(57) Abstract

The invention relates to novel compounds from the class of the macrolide antibiotic oleandomycin of general formula (I) wherein R¹ has the individual meaning of -CH₂CH₃ group, of a fragment of formula (II), together with R² has the meaning of a fragment of formula (III) or together with R⁴ has the meaning of a fragment of formula (IV) or a fragment of formula (V), R² together with R³ has the meaning of a ketone or together with R¹ has the meaning of a fragment of formula (III), R³ has the individual meaning of OH group or together with R² has the meaning of a ketone, R⁴ has the individual meaning of a methyl group, or together with R¹ has the meaning of a fragment of formula (IV) or of a fragment of formula (V), R⁵ has the individual meaning of hydrogen or a benzyloxycarbonyl group, R⁶ has the individual meaning of hydrogen, a methyl group or a benzyloxycarbonyl group, to intermediates for the preparation thereof, to a process for preparing them as well as to pharmaceutically acceptable addition salts thereof with inorganic or organic acids.



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NOVEL DERIVATIVES FROM THE CLASS OF OLEANDOMYCIN

1) Technical Field

A 61 K 31/70, C 0 7H 17/08

2) Technical Problem

The invention relates to novel compounds from the class of the macrolide antibiotic oleandomycin, to intermediates for the preparation thereof, to a process for preparing them as well as to pharmaceutically acceptable addition salts thereof with inorganic or organic acids.

3) Prior Art

Oleandomycin is a macrolide antibiotic (US patent 2,757,123) having an activity spectrum similar to that of erythromycin A. The oleandomycin structure is characterized by a 14-member lactone ring with a keto group in C-9 position, by the sugar desosamin in C-5 position and by the sugar oleandrose in C-3 position as well as by three OH groups. It differs from other polyoxo macrolides by an exocyclic epoxide ring on C-8 atom. Earlier investigations (JACS **82**, 3225-3227, 1960; JOC **51**, 5397-5400, 1986) showed its exceptional sensitivity both in acidic and basic conditions. In an acidic medium C-8 epoxide is opened, oleandrose is cleaved and a contraction of the aglycone ring takes place. The action of a base causes a dehydration of H-10 and OH-11 under the generation of C-10/C-11 double bond to give anhydrooleandomycin. All these transformations cause a loss of the antibiotic action.

It is known that similar transformations at erythromycin A with OH groups participating are successfully inhibited by *O*-methylation thereof (Watanabe Y. and al, US patent 4,331,803, 5/1982). By the reaction of erythromycin A with benzyloxy-carbonyl chloride and then by methylation of the obtained 2'-*O*,3'-*N*-bis(benzyloxy-

carbonyl)-derivatives, elimination of protecting groups and *N*-methylation, there are obtained, in addition to 6-*O*-methyl erythromycin (CLARITHROMYCIN), significant amounts of 11-*O*-methyl erythromycin and polysubstituted analogues (Morimo S. et al, J. Antibiotics 1984, 37, 187). Clarithromycin is significantly more stable in an acidic medium than erythromycin A and shows enhanced *in vitro* activity against Gram positive bacterial strains (Kirst H. A. et al, Antimicrobial Agents and Chemother., 1989, 1419). Similarly, also a series of *O*-methyl derivatives of azythromycin was synthesised (Kobrehel G. et al, US patent 5,250,518, 5/1993).

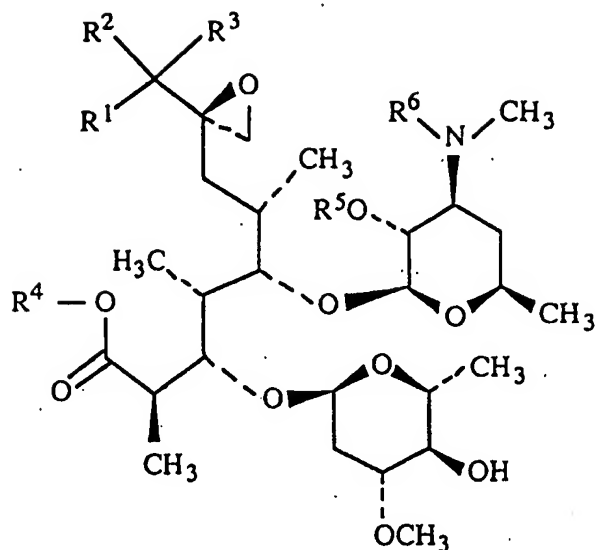
Our efforts to inhibit the formation of an inactive anhydrooleandomycin by *O*-methylation of C-1 hydroxyl group, retroaldol fragmentation, dehydration and isomerisation, led to a series of linear and cyclic derivatives of oleandomycin, not yet disclosed so far, which may serve as intermediates for chimeric oleandomycins with potential biological action.

The synthesis of these derivatives involves a reaction of oleandomycin with benzyloxycarbonyl chloride to obtain 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-oleandomycin, a reaction with methyl iodide in the presence of sodium hydride, an elimination of protecting groups on 2' and 3' positions and reductive 3'-*N*-methylation.

Oleandomycin derivatives according to the present invention and their pharmaceutically acceptable addition salts with inorganic or organic acids, methods and intermediates for the preparation thereof have not been disclosed in Prior Art.

4) Description of the Invention with Examples

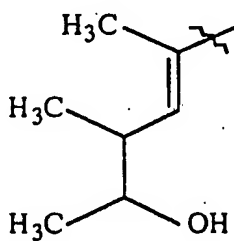
Novel derivatives of oleandomycin of the general formula (I)



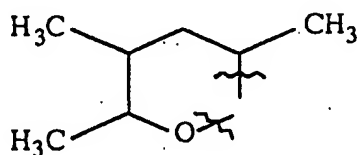
I

wherein

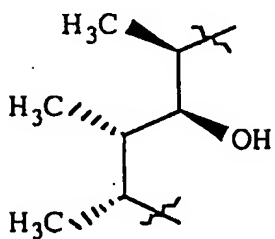
R^1 has the individual meaning of $-\text{CH}_2\text{CH}_3$ group, of a fragment of the formula (II), together with R^2 has the meaning of a fragment of the formula (III) or together with R^4 has the meaning of a fragment of the formula (IV) or a fragment of the formula (V)



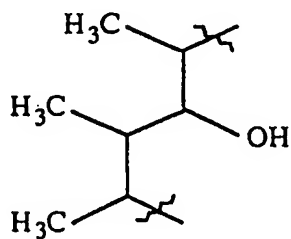
II



III



IV



V

R^2 together with R^3 has the meaning of a ketone or together with R^1 has the meaning of a fragment of the formula (III),

R^3 has the individual meaning of OH group or together with R^2 has the meaning of a ketone,

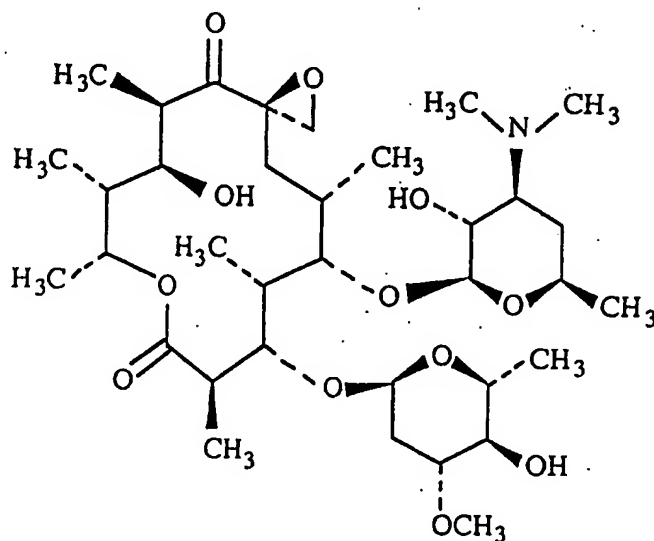
R^4 has the individual meaning of a methyl group, or together with R^1 has the meaning of a fragment of the formula (IV) or of a fragment of the formula (V),

R^5 has the individual meaning of hydrogen or a benzyloxycarbonyl group,

R^6 has the individual meaning of hydrogen, a methyl group or a benzyloxycarbonyl group,

and their pharmaceutically acceptable addition salts with inorganic or organic acids, are obtained as follows.

Step 1:



VI

By subjecting oleandomycin of the formula (VI) to a reaction with benzyloxycarbonyl chloride in the presence of bases, preferably sodium hydrogen carbonate, in a solvent inert in the reaction, preferably benzene or toluene, there is obtained 2'-O,3'-N-bis(benzyloxycarbonyl)-3'-N-demethyl-oleandomycin of the general formula (I), wherein R^1 together with R^4 has the meaning of a fragment of the formula (IV), R^2

together with R^3 has the meaning of a ketone and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group.

Step 2:

By a reaction of 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-oleandomycin from Step 1 with 1.3-3.25 equivalents of the corresponding methylation agent, preferably methyl iodide, and 1.1-3.75 equivalents of the corresponding base, preferably sodium hydride, at a temperature from -15°C to room temperature, preferably at 0-5°C, in an appropriate aprotic solvent or solvent mixture, preferably DMSO-THF = 1:1, and by separation on a silica gel column in the system toluene-ethyl acetate = 1:1 there is obtained

a compound **2A** of the general formula (I), wherein R^1 has the individual meaning of -CH₂CH₃ group, R^2 together with R^3 has the meaning of a ketone, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group,

a compound **2B** of the general formula (I), wherein R^1 together with R^4 has the meaning of a fragment of the formula (V), R^2 together with R^3 has the meaning of a ketone and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group, and

a compound **2C** of the general formula (I), wherein R^1 has the individual meaning of a fragment of the formula (II), R^2 together with R^3 has the meaning of a ketone, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group.

The relative ratio of chromatographically homogenous products depends upon the equimolar ratio of reactants.

Step 3:

Each of the oleandomycin derivatives from Step 2 is separately subjected to a hydrogenolysis reaction in order to eliminate protecting benzyloxycarbonyl groups in 2' and 3' positions according to the method by E. H. Flynn et al (Journal of American Chemical Society, 77, 3104, 1950). Hydrogenolysis is carried out in a lower alcohol solution, preferably in ethanol, in the presence of NaOAc/HOAc buffer (pH 5), with a catalyst such as palladium black or palladium on carbon, under hydrogen pressure of 10^5 Pa at room temperature to obtain, respectively,

in case of **2A**, a compound **3A** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **2A** and R^5 and R^6 are the same and have the meaning of hydrogen, and

in case of **2B**, a compound **3B** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **2B** and R^5 and R^6 are the same and have the meaning of hydrogen, and

in case of **2C**, a compound **3C** of the general formula (I), wherein R^1 together with R^2 has the meaning of a fragment of the formula (III), R^3 is an OH group, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of hydrogen.

Step 4:

Each of the 3'-*N*-demethyl derivatives of oleandomycin from Step 3 is subjected to reductive *N*-methylation in 3' position with 1-6.2 equivalents of formaldehyde (36%) in the presence of 1-4.2 equivalents of formic acid (98-100%) or some other hydrogen source, in a solvent inert in the reaction such as halogenated hydrocarbons, lower alcohols or lower ketones, preferably chloroform, at the reflux temperature of the reaction mixture, to obtain, respectively,

in case of **3A**, a compound **4A** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **2A**, R^5 is hydrogen and R^6 is a methyl group, and

in case of **3B**, a compound **4B** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **2B**, R^5 is hydrogen and R^6 is a methyl group, and

in case of **3C**, a compound **4C** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **3C**, R^5 is hydrogen and R^6 is a methyl group.

Fragments of the formulas (II), (III) and (V) are shown without space orientation of the bonds and define all combinations of orientation of bonds in order to comprise all possible stereoconfigurations, i.e. epimers.

Pharmaceutically acceptable addition salts which are also an object of the present invention, are obtained by reacting novel oleandomycin derivatives of the general formula (I) with an at least equimolar amount of a corresponding inorganic or organic acid such as hydrochloric, hydroiodic, sulfuric, phosphoric, acetic, propionic, trifluoroacetic, maleic, citric, stearic, succinic, ethylsuccinic, methanesulfonic, benzenesulfonic, p-toluenesulfonic, laurylsulfonic acids etc., in a solvent inert in the reaction. Addition salts are isolated by filtration if insoluble in the solvent inert in the reaction, by precipitation by means of non-solvents or evaporation of solvents, most often by a lyophilization process.

The process for preparing novel derivatives of oleandomycin is illustrated by the following non-limiting Examples.

Example 1

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-oleandomycin

To a solution of oleandomycin (50.98 g, 0.0741 mol) in benzene (385 ml) NaHCO_3 was added (226.74 g; 2.6990 mol) and the reaction mixture was heated under stirring

to the reflux temperature (55-60°C). 95% benzyloxycarbonylchloride (312 ml; 354.20 g; 2.0762 mol) was added drop by drop for 4 hours under stirring. The reaction mixture was stirred for further 24 hours at the same temperature and left for 42 hours at room temperature. After the filtration the precipitate was washed with benzene (75 ml) and the benzene solution was extracted three times with 100 ml of 0.25 *N* HCl and once with 100 ml water. The benzene solution was dried over CaCl₂, filtered and evaporated under reduced pressure to give a viscous oily residue (306.4 g), which was purified by low pressure chromatography on a column of silica gel 60 (230-400 mesh ASTM). To this effect the crude oily product was applied to a silica gel column (500 g) under a nitrogen pressure of 0.5.10⁵ Pa. The excess of the reagent was removed by passing CH₂Cl₂ (1400 ml) and then there was obtained 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethyl-oleandomycin (19.77 g) using the system methylene chloride-methanol 95:5 (1000 ml) and evaporation of fractions containing the chromatographically homogenous title product with the following physico-chemical constants:

EI-MS *m/z* 943

TLC, methylene chloride-methanol, 95 : 5

R_f 0.397

toluene-ethyl acetate, 1 : 1

R_f 0.420

(IR) (KBr) cm⁻¹ 3480, 2980, 2940, 1755, 1710, 1460, 1385, 1325, 1295, 1255, 1115, 1060, 1005, 990, 760, 700.

¹H NMR (300 MHz, CDCl₃) δ 7.35-7.28 (Ph), 5.11, 5.09 (CH₂-Ph), 5.58 (H-13), 4.95 (H-1"), 4.66 (H-2'), 4.49 (H-1'), 4.41 (H-3'), 3.80 (H-11), 3.70 (H-5"), 3.46 (H-3"), 3.40 (3"-OCH₃), 3.40 (H-5), 3.15 (H-4"), 3.00 (H-10), 3.00 (H-8a), 2.85 (H-8b), 2.83 (H-2), 2.80 (3'-NHCH₃), 2.35 (H-2"a), 2.24 (H-7a), 1.73 (H-7b), 1.69 (H-6), 1.69 (H-4'a), 1.65 (H-4), 1.62 (H-12), 1.53 (H-2"b), 1.31 (5"-CH₃), 1.26 (13-CH₃), 1.22 (5'-CH₃), 1.20 (2-CH₃), 1.03 (6-CH₃), 1.03 (10-CH₃), 0.89 (4-CH₃), 0.86 (12-CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 214.2 (C-9), 176.4 (C-1), 156.4, 156.0 (OCO), 154.4, 154.3 (NCO), 136.6 (*O* Ph), 134.9 (*N* Ph), 128.5-127.6 (Ph), 101.8 (C-1'), 99.0 (C-1"), 86.1 (C-5), 80.1 (C-3), 77.6 (C-3"), 75.8 (C-4"), 74.6 (C-2'), 70.2 (C-13), 69.2 (C-5'), 68.7 (C-11), 68.5 (C-5"), 69.6, 69.5, 67.1, 66.9 (CH₂-Ph), 61.9 (C-8), 56.2 (3"-OCH₃), 54.7 (C-3'), 50.2 (8-CH₂), 44.5 (C-10), 44.3 (C-2), 42.2 (C-4), 41.4 (C-12), 35.4 (C-

4'), 33.8 (C-6), 33.6 (C-2''), 30.0 (C-7), 28.9 (3'-NHCH₃), 20.4 (5'-CH₃), 18.1 (13-CH₃), 17.6 (5''-CH₃), 9.0 (4-CH₃), 8.5 (12-CH₃), 6.4 (10-CH₃).

Example 2

Method A

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-11,12,13-trisnor-1-methoxy-10,11-seco-oleandomicyn (2A)

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-*epi*-oleandomicyn (2B)

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-1-methoxy-10,11-anhydro-1,13-seco-oleandomicyn (2C)

To a solution of 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-oleandomicyn (6.00 g, 6.4 mmol) from Example 1 in a dimethylsulfoxide-tetrahydrofuran mixture (1:1, 48 ml) cooled to 0-5°C, methyl iodide (1.32 ml; 20.7 mmol) diluted with a dimethylsulfoxide-tetrahydrofuran mixture (1:1, 12 ml) and 60% sodium hydride in mineral oil (0.76 g; 17.5 mmol) were added step by step for 1 hour. The reaction mixture was stirred for further 2 hours at the same temperature. The reaction was interrupted by addition of triethyl amine (10 ml), it was stirred for 10 minutes, a saturated NaCl solution (80 ml) was added, it was stirred for further 10 minutes and the inorganic part was filtered off. The filtrate was extracted with ethyl acetate (80 ml), the organic layer was washed two more times with a saturated NaCl solution (80 ml) and dried over K₂CO₃. After filtration and evaporation under reduced pressure a yellowish amorphous precipitate (5.36 g) was obtained. By chromatography on a silica gel column using a system toluene-ethyl acetate = 1:1, from the reaction mixture (2.82 g) a chromatographically homogenous compound **2A** (0.40 g), a chromatographically homogenous compound **2B** (0.12 g), and a chromatographically homogenous compound **2C** (0.39 g), characterized by the following physico-chemical constants, were isolated.

2A

TLC, methylene chloride-methanol, 95 : 5

R_f 0.587

toluene-ethyl acetate, 1 : 1

R_f 0.687

(IR) (KBr) cm^{-1} 3480, 2980, 2940, 1750, 1710, 1455, 1385, 1335, 1295, 1260, 1165, 1110, 1055, 1005, 830, 790, 760, 700.

^1H NMR (300 MHz, CDCl_3) δ 7.35-7.27 (Ph), 5.12, 5.09 ($\text{CH}_2\text{-Ph}$), 4.89 (H-1"), 4.64 (H-2'), 4.49 (H-1'), 4.46 (H-3'), 3.90 (H-3), 3.70 (1-OCH₃), 3.70 (H-5"), 3.61 (H-5'), 3.45 (H-3"), 3.41 (H-5), 3.40 (3"-OCH₃), 3.12 (H-4"), 2.85 (3'-NHCH₃), 2.79 (H-2), 2.76 (H-8a), 2.74 (H-8b), 2.56 (H-7a), 2.39 (H-10a), 2.34 (H-10b), 2.27 (H-2"a), 1.90 (H-6), 1.73 (H-4), 1.70 (H-4'a), 1.61 (H-4'b), 1.46 (H-2"b), 1.22 (5'-CH₃), 1.21 (5"-CH₃), 1.18 (2-CH₃), 1.16 (H-7b), 1.03 (6-CH₃), 1.03 (10-CH₃), 0.90 (4-CH₃).

^{13}C NMR (75 MHz, CDCl_3) δ 209.5 (C-9), 175.2 (C-1), 156.1, 155.7 (OCO), 154.2, 154.1 (NCO), 136.3 (O Ph), 134.9 (N Ph), 129.2-127.3 (Ph), 100.9 (C-1'), 97.8 (C-1"), 82.9 (C-5), 79.7 (C-3), 77.8 (C-3"), 75.5 (C-4"), 74.3 (C-2'), 68.2 (C-5'), 68.2 (C-5"), 69.3, 69.1, 67.1, 66.9 ($\text{CH}_2\text{-Ph}$), 62.1 (C-8), 56.1 (3"-OCH₃), 54.5 (C-3'), 51.5 (1-OCH₃), 49.9 (8-CH₂), 42.0 (C-2), 39.4 (C-4), 35.9 (C-4'), 33.9 (C-2"), 32.4 (C-6), 31.7 (C-7), 29.1 (10-CH₂), 28.4 (3'-NHCH₃), 20.3 (5'-CH₃), 17.6 (6-CH₃), 17.4 (5"-CH₃), 11.9 (2-CH₃), 9.7 (4-CH₃), 7.1 (10-CH₃).

2B

TLC, methylene chloride-methanol, 95 : 5

R_f 0.447

toluene-ethyl acetate, 1 : 1

R_f 0.520

(IR) (KBr) cm^{-1} 3480, 2970, 2930, 1750, 1725, 1700, 1450, 1380, 1330, 1295, 1255, 1160, 1110, 1060, 990, 785, 755, 695, 665.

^1H NMR (300 MHz, CDCl_3) δ 7.38-7.27 (Ph), 5.13, 5.08 ($\text{CH}_2\text{-Ph}$), 4.88 (H-13), 4.88 (H-1"), 4.66 (H-2'), 4.47 (H-3'), 4.41 (H-1'), 3.85 (H-11), 3.68 (H-5"), 3.66 (H-3), 3.62 (H-5'), 3.43 (H-3"), 3.40 (3"-OCH₃), 3.33 (H-5), 3.26 (H-10), 3.13 (H-4"), 2.83 (H-8a), 2.83 (H-8b), 2.81 (3'-NHCH₃), 2.67 (H-2), 2.64 (H-7a), 2.34 (H-2"a), 1.76 (H-6), 1.72 (H-12), 1.70 (H-4'a), 1.70 (H-4), 1.62 (H-4'b), 1.50 (H-2"b), 1.32 (H-7b), 1.28 (13-CH₃), 1.27 (5"-CH₃), 1.22 (5'-CH₃), 1.18 (2-CH₃), 1.12 (6-CH₃), 1.06 (10-CH₃), 1.03 (12-CH₃), 0.96 (4-CH₃).

^{13}C NMR (75 MHz, CDCl_3) δ 211.3 (C-9), 174.9 (C-1), 156.5, 156.1 (OCO), 154.5, 154.4 (NCO), 136.6 (O Ph), 135.0 (N Ph), 128.5-127.6 (Ph), 101.6 (C-1'), 98.8 (C-1"), 83.9 (C-5), 79.8 (C-3), 77.7 (C-3"), 75.8 (C-4"), 74.6 (C-2'), 73.2 (C-13), 70.1 (C-11),

68.5 (C-5''), 68.3 (C-5'), 69.6, 69.4, 67.0, 66.9 (CH₂-Ph), 61.5 (C-8), 56.2 (3''-OCH₃), 54.6 (C-3'), 51.2 (8-CH₂), 44.6 (C-2), 43.3 (C-4), 42.4 (C-10), 40.5 (C-12), 35.5 (C-4'), 33.7 (C-2''), 32.0 (C-6), 30.7 (C-7), 28.5 (3'-NHCH₃), 20.4 (5'-CH₃), 19.8 (6-CH₃), 17.5 (5''-CH₃), 15.2 (13-CH₃), 13.6 (2-CH₃), 10.5 (12-CH₃), 10.2 (10-CH₃), 9.2 (4-CH₃).

2C

TLC, methylene chloride-methanol, 95 : 5

R_f 0.420

toluene-ethyl acetate, 1 : 1

R_f 0.360

(IR) (KBr) cm⁻¹ 3460, 2970, 2930, 1740, 1690, 1450, 1380, 1330, 1290, 1250, 1160, 1110, 1050, 1000, 785, 755, 695, 665.

¹H NMR (300 MHz, CDCl₃) δ 7.34-7.20 (Ph), 6.74 (H-11), 5.10, 5.09 (CH₂-Ph), 4.84 (H-1''), 4.64 (H-2'), 4.51 (H-1'), 4.43 (H-3'), 3.94 (H-3), 3.84 (H-13), 3.72 (H-5''), 3.58 (H-5'), 3.44 (1-OCH₃), 3.42 (H-3''), 3.38 (3''-OCH₃), 3.29 (H-5), 3.09 (H-4''), 2.85 (3'-NHCH₃), 2.83 (H-8a), 2.83 (H-7a), 2.75 (H-8b), 2.73 (H-12), 2.65 (H-2), 2.19 (H-2''a), 1.84 (10-CH₃), 1.78 (H-4), 1.74 (H-4'a), 1.69 (H-6), 1.39 (H-2''b), 1.24 (5''-CH₃), 1.22 (H-7b), 1.22 (13-CH₃), 1.22 (5'-CH₃), 1.08 (12-CH₃), 1.07 (2-CH₃), 1.00 (6-CH₃), 0.82 (4-CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 199.0 (C-9), 175.7 (C-1), 156.3, 156.0 (OCO), 154.6, 154.4 (NCO), 147.7 (C-11), 136.5 (O Ph), 135.2 (N Ph), 134.1 (C-10), 128.7-127.4 (Ph), 101.0 (C-1'), 97.4 (C-1''), 82.6 (C-5), 79.6 (C-3), 78.0 (C-3''), 75.8 (C-4''), 74.3 (C-2'), 70.3 (C-13), 68.6 (C-5'), 68.3 (C-5''), 69.6, 69.3, 67.1, 66.9 (CH₂-Ph), 62.0 (C-8), 56.1 (3''-OCH₃), 55.1 (C-3'), 51.7 (1-OCH₃), 50.0 (8-CH₂), 41.0 (C-12), 40.3 (C-2), 38.6 (C-4), 37.0 (C-7), 35.4 (C-4'), 33.9 (C-2''), 33.1 (C-6), 28.9 (3'-NHCH₃), 20.9 (5'-CH₃), 20.7 (13-CH₃), 17.5 (5''-CH₃), 16.8 (6-CH₃), 14.0 (2-CH₃), 11.5 (10-CH₃), 10.1 (12-CH₃), 9.4 (4-CH₃).

Example 2

Method B

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-11,12,13-trisnor-1-methoxy-10,11-seco-oleandomicyn (2A)

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-1-methoxy-10,11-anhydro-1,13-seco-oleandomicyn (2C)

To a solution of 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-oleandomicyn (6.00 g, 6.4 mmol) from Example 1 in a dimethylsulfoxide-tetrahydrofuran mixture (1:1, 12 ml) cooled to 0-5°C, methyl iodide (1.32 ml; 20.7 mmol) diluted with a dimethylsulfoxide-tetrahydrofuran mixture (1:1, 12 ml) and 60% sodium hydride in mineral oil (1.04 g; 23.9 mmol) were added step by step for 1 hour. The reaction mixture was stirred for further 2 hours at the same temperature. The reaction was interrupted by addition of triethyl amine (10 ml), it was stirred for 10 minutes, a saturated NaCl solution (80 ml) was added, it was stirred for further 10 minutes and the inorganic part was filtered off. The filtrate was extracted with ethyl acetate (80 ml), the organic layer was washed two more times with a saturated NaCl solution (80 ml) and dried over K₂CO₃. After filtration and evaporation under reduced pressure, a yellowish amorphous precipitate (5.90 g) was obtained. By chromatography on a silica gel column using the system toluene-ethyl acetate = 1:1, from the reaction mixture (2.95 g) a chromatographically homogenous compound 2A (0.12 g) and a chromatographically homogenous compound 2C (0.40 g), characterized by the physico-chemical constants as given in Example 2, Method A, were isolated.

Example 2

Method C

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-11,12,13-trisnor-1-methoxy-10,11-seco-oleandomicyn (2A)

2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-*epi*-oleandomicyn (2B)

To a solution of 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyl-oleandomicyn (6.00 g, 6.4 mmol) from Example 1 in a dimethylsulfoxide-tetrahydrofuran mixture (1:1, 48 ml) cooled to 0-5°C, methyl iodide (0.52 ml; 8.1 mmol) diluted with a dimethylsulfoxide-tetrahydrofuran mixture (1:1, 12 ml) and 60% sodium hydride in mineral oil (0.30 g; 6.8 mmol) were added step by step for 1 hour. The reaction mixture was

stirred for further 2 hours at the same temperature. The reaction was interrupted by addition of triethyl amine (10 ml), it was stirred for 10 minutes, a saturated NaCl solution (80 ml) was added, it was stirred for further 10 minutes and the inorganic part was filtered off. The filtrate was extracted with ethyl acetate (80 ml), the organic layer was washed two more times with a saturated NaCl solution (80 ml) and dried over K_2CO_3 . After filtration and evaporation under reduced pressure, a yellowish amorphous precipitate (5.59 g) was obtained. By chromatography on a silica gel column using the system toluene-ethyl acetate = 1:1, from the reaction mixture (2.80 g) a chromatographically homogenous compound **2A** (0.44 g) and a chromatographically homogenous compound **2B** (0.66 g), characterized by the physico-chemical constants as given in Example 2, Method A, were isolated.

Example 3

3'-N-demethyl-11,12,13-trisnor-1-methoxy-10,11-seco-oleandomicyn (3A)

The product **2A** (2.65 g, 3 mmol) was dissolved in ethanol (42 ml), the pH was adjusted to 6.8 with a buffer pH 5 (0.19 ml HOAc, 0.30 g NaOAc and 10 ml water), Pd/C 10% (0.28 g) was added and the reaction mixture was hydrogenated under stirring for 3.5 hours in an autoclave at a hydrogen pressure of 10^5 Pa at room temperature. The catalyst was filtered off, the filtrate was evaporated to a viscous syrup, $CHCl_3$ (50 ml) and water (50 ml) were added, the pH of the mixture was adjusted with 20% NaOH to 9.0, the layers were separated and the aqueous extract was extracted three more times with $CHCl_3$ (50 ml). Combined organic extracts were dried over K_2CO_3 , filtered, evaporated under reduced pressure, optionally purified by chromatography on a silica gel column using the system chloroform-methanol-conc. ammonia 60:10:1 to give the title product (1.45 g) with the following physico-chemical constants:

EI-MS m/z 604

TLC, chloroform-methanol-conc. ammonia, 60 : 10 : 1 Rf 0.602

methylen chloride-methanol-conc. ammonia, 90 : 9 : 1.5 Rf 0.358

(IR) (KBr) cm^{-1} 3310, 2970, 2930, 1730, 1715, 1465, 1455, 1380, 1260, 1195, 1155, 1070, 1045, 1005, 985, 900, 755, 665.

^1H NMR (300 MHz, CDCl_3) δ 4.90 (H-1"), 4.27 (H-1'), 3.99 (H-3), 3.74 (H-5"), 3.70 (1-OCH₃), 3.55 (H-5'), 3.46 (H-5), 3.42 (H-3"), 3.40 (3"-OCH₃), 3.19 (H-2'), 3.17 (H-4"), 2.81 (H-2), 2.77 (H-8a), 2.74 (H-8b), 2.67 (H-7a), 2.52 (H-3'), 2.41 (H-10a), 2.40 (3'-NHCH₃), 2.35 (H-10b), 2.29 (H-2"a), 2.05 (H-6), 1.93 (H-4'a), 1.87 (H-4), 1.49 (H-2"b), 1.28 (5"-CH₃), 1.21 (2-CH₃), 1.20 (H-4'b), 1.20 (5'-CH₃), 1.10 (H-7b), 1.04 (4-CH₃), 1.02 (6-CH₃), 1.02 (10-CH₃).

^{13}C NMR (75 MHz, CDCl_3) δ 209.9 (C-9), 175.7 (C-1), 103.3 (C-1'), 98.1 (C-1"), 82.3 (C-5), 80.2 (C-3), 77.8 (C-3"), 75.4 (C-4"), 73.4 (C-2'), 68.5 (C-5'), 68.4 (C-5"), 62.1 (C-8), 59.9 (C-3'), 56.2 (3"-OCH₃), 51.4 (1-OCH₃), 49.8 (8-CH₂), 42.0 (C-2), 39.1 (C-4), 36.6 (C-4'), 33.9 (C-2"), 32.7 (3'-NHCH₃), 32.6 (C-7), 32.3 (C-6), 29.0 (10-CH₂), 20.6 (5'-CH₃), 17.2 (5"-CH₃), 17.0 (6-CH₃), 11.7 (2-CH₃), 10.3 (4-CH₃), 6.9 (10-CH₃).

Example 4

3'-N-demethyl-*epi*-oleandomycin (3B)

The product **2B** (1.42 g, 1.5 mmol) was dissolved in ethanol (23 ml), the pH was adjusted to 6.8 with a buffer pH 5 (0.19 ml HOAc, 0.30 g NaOAc and 10 ml water), Pd/C 10% (0.15 g) was added and the reaction mixture was hydrogenated under stirring for 4.5 hours in an autoclave at a hydrogen pressure of 10^5 Pa at room temperature. The isolation was carried out as in Example 3. After evaporation under reduced pressure, the product was optionally purified by chromatography on a silica gel column using the system chloroform-methanol-conc. ammonia 60:10:1 to give the title product (0.99 g) with the following physico-chemical constants:

EI-MS m/z 674

TLC, chloroform-methanol-conc. ammonia, 60 : 10 : 1 R_f 0.370

methylene chloride-methanol-conc. ammonia, 90 : 9 : 1.5 R_f 0.170

(IR) (KBr) cm^{-1} 3450, 2980, 2940, 2900, 1730, 1715, 1465, 1455, 1385, 1255, 1190, 1155, 1070, 1050, 1000, 875, 755, 670.

^1H NMR (300 MHz, CDCl_3) δ 5.09 (H-13), 4.90 (H-1''), 4.19 (H-1'), 3.74 (H-11), 3.72 (H-5''), 3.71 (H-3), 3.54 (H-5'), 3.44 (H-5), 3.44 (H-3''), 3.41 (3''-OCH₃), 3.23 (H-10), 3.17 (H-2'), 3.15 (H-4''), 2.88 (H-8a), 2.88 (H-8b), 2.77 (H-2), 2.53 (H-3'), 2.41 (3'-NHCH₃), 2.34 (H-2''a), 2.21 (H-7a), 1.95 (H-4'a), 1.94 (H-6), 1.85 (H-7b), 1.70 (H-4), 1.53 (H-12), 1.51 (H-2''b), 1.30 (5''-CH₃), 1.27 (13-CH₃), 1.21 (5'-CH₃), 1.20 (2-CH₃), 1.18 (H-4'b), 1.13 (6-CH₃), 1.10 (12-CH₃), 1.09 (10-CH₃), 1.09 (4-CH₃).

^{13}C NMR (75 MHz, CDCl_3) δ 212.2 (C-9), 174.5 (C-1), 102.9 (C-1'), 99.9 (C-1''), 81.5 (C-3), 81.1 (C-5), 77.7 (C-3''), 75.6 (C-4''), 73.9 (C-2'), 71.1 (C-13), 70.0 (C-11), 68.6 (C-5''), 68.5 (C-5'), 61.2 (C-8), 59.6 (C-3'), 56.3 (3''-OCH₃), 49.9 (8-CH₂), 44.6 (C-2), 42.6 (C-12), 41.8 (C-10), 40.5 (C-4), 36.9 (C-4'), 33.9 (C-2''), 32.9 (3'-NHCH₃), 31.7 (C-7), 30.6 (C-6), 20.7 (5'-CH₃), 20.2 (6-CH₃), 17.6 (5''-CH₃), 16.7 (13-CH₃), 14.8 (2-CH₃), 10.1 (12-CH₃), 9.9 (4-CH₃), 9.2 (10-CH₃).

Example 5

3'-N-demethyl-1-methoxy-1,13-seco-oleandomicyn-9,13-hemiketal (3C)

The product 2C (1.28 g, 1.3 mmol) was dissolved in ethanol (21 ml), the pH was adjusted to 6.8 with a buffer pH 5 (0.19 ml HOAc, 0.30 g NaOAc and 10 ml water), Pd/C 10% (0.18 g) was added and the reaction mixture was hydrogenated under stirring for 6 hours in an autoclave at a hydrogen pressure of 10^5 Pa at room temperature. The isolation was carried out as in Example 3. After evaporation under reduced pressure, the product was optionally purified by chromatography on a silica gel column using the system chloroform-methanol-conc. ammonia 60:10:1 to give the title product (0.81 g) with the following physico-chemical constants:

EI-MS m/z 690

TLC, chloroform-methanol-conc. ammonia, 60 : 10 : 1 Rf 0.556

methylen chloride-methanol-conc. ammonia, 90 : 9 : 1.5 Rf 0.302

(IR) (KBr) cm^{-1} 3470, 2980, 2940, 2900, 1735, 1465, 1455, 1385, 1265, 1205, 1160, 1075, 1040, 1000, 900, 760, 670.

^1H NMR (300 MHz, CDCl_3) δ 4.84 (H-1''), 4.30 (H-1'), 4.15 (H-13), 4.03 (H-3), 3.76 (H-5''), 3.71 (1-OCH₃), 3.56 (H-5'), 3.45 (H-3''), 3.42 (H-5), 3.39 (3''-OCH₃), 3.18 (H-

2'), 3.14 (H-4''), 2.84 (H-8a), 2.79 (H-2), 2.63 (H-8b), 2.54 (H-3'), 2.44 (H-7a), 2.41 (3'-NHCH₃), 2.26 (H-2''a), 2.10 (H-10), 1.96 (H-6), 1.94 (H-4'a), 1.92 (H-4), 1.85 (H-11a), 1.66 (H-12), 1.47 (H-2''b), 1.40 (H-11b), 1.36 (H-7b), 1.28 (5''-CH₃), 1.22 (5'-CH₃), 1.19 (H-4'b), 1.16 (2-CH₃), 1.04 (6-CH₃), 1.00 (13-CH₃), 0.98 (12-CH₃), 0.98 (4-CH₃), 0.81 (10-CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 175.8 (C-1), 103.7 (C-1'), 98.1 (C-1''), 97.4 (C-9), 82.7 (C-5), 80.6 (C-3), 78.0 (C-3''), 75.6 (C-4''), 74.0 (C-2'), 68.7 (C-5'), 68.5 (C-5''), 66.9 (C-13), 60.5 (C-8), 60.1 (C-3'), 56.2 (3''-OCH₃), 51.7 (1-OCH₃), 49.5 (8-CH₂), 41.7 (C-2), 38.5 (C-4), 36.9 (C-4'), 35.5 (C-11), 34.0 (C-2''), 32.9 (3'-NHCH₃), 32.0 (C-12), 31.7 (C-6), 30.8 (C-7), 27.4 (C-10), 20.9 (5'-CH₃), 18.3 (4-CH₃), 18.0 (13-CH₃), 17.4 (5''-CH₃), 15.9 (10-CH₃), 11.6 (12-CH₃), 11.0 (2-CH₃), 10.5 (6-CH₃).

Example 6

11,12,13-trisnor-1-methoxy-10,11-seco-oleandomicyn (4A)

To a solution of 3'-N-demethyl-11,12,13-trisnor-1-methoxy-10,11-seco-oleandomicyn from Example 3 (0.90 g; 1.5 mmol) in CHCl₃ (60 ml), 36% formaldehyde (0.236 ml; 8.5 mmol) and 98-100% formic acid (0.217 ml; 5.8 mmol) were added. The reaction mixture was stirred for 3.5 hours under reflux, cooled to room temperature, poured into water (60 ml), the pH of the mixture was adjusted with 2N NaOH to 9.0, the layers were separated and the aqueous layer was extracted three more times with CHCl₃ (30 ml). Combined organic extracts were dried over K₂CO₃, filtered, evaporated under reduced pressure, optionally purified on a silica gel column using the system chloroform-methanol-conc. ammonia 60:10:1 to give the title product (0.97 g) with the following physico-chemical constants:

EI-MS m/z 618

TLC, chloroform-methanol-conc. ammonia, 60 : 10 : 1 R_f 0.787

methylen chloride-methanol-conc. ammonia, 90 : 9 : 1.5 R_f 0.575

(IR) (KBr) cm⁻¹ 3450, 2970, 2930, 1735, 1715, 1460, 1455, 1380, 1260, 1195, 1160, 1075, 1045, 1000, 795, 755.

^1H NMR (300 MHz, CDCl_3) δ 4.92 (H-1"), 4.27 (H-1'), 4.00 (H-3), 3.77 (H-5"), 3.69 (1-OCH₃), 3.48 (H-5'), 3.46 (H-3"), 3.41 (H-5), 3.40 (3"-OCH₃), 3.23 (H-2'), 3.14 (H-4"), 2.83 (H-2), 2.78 (H-8a), 2.75 (H-8b), 2.66 (H-7a), 2.49 (H-3'), 2.43 (H-10a), 2.28 (3'-N(CH₃)₂), 2.37 (H-10b), 2.31 (H-2"a), 2.04 (H-6), 1.88 (H-4), 1.65 (H-4'a), 1.48 (H-2"b), 1.29 (5"-CH₃), 1.24 (H-4'b), 1.23 (2-CH₃), 1.20 (5'-CH₃), 1.20 (H-7b), 1.12 (4-CH₃), 1.05 (6-CH₃), 1.03 (10-CH₃).

^{13}C NMR (75 MHz, CDCl_3) δ 209.9 (C-9), 175.6 (C-1), 104.0 (C-1'), 98.5 (C-1"), 83.1 (C-5), 80.5 (C-3), 77.9 (C-3"), 75.7 (C-4"), 70.1 (C-2'), 68.9 (C-5'), 68.2 (C-5"), 65.2 (C-3'), 62.1 (C-8), 56.0 (3"-OCH₃), 51.4 (1-OCH₃), 49.9 (8-CH₂), 42.6 (C-2), 40.0 (3'-N(CH₃)₂), 39.6 (C-4), 33.9 (C-2"), 31.9 (C-6), 31.8 (C-7), 29.0 (10-CH₂), 28.4 (C-4'), 20.8 (5'-CH₃), 17.5 (6-CH₃), 17.2 (5"-CH₃), 12.7 (2-CH₃), 10.1 (4-CH₃), 7.0 (10-CH₃).

Example 7

***epi*-Oleandomycin (4B)**

To a solution of 3'-N-demethyl-*epi*-oleandomycin from Example 4 (1.12 g; 1.7 mmol) in CHCl_3 (75 ml), 36% formaldehyde (0.291 ml; 10.5 mmol) and 98-100% formic acid (0.267 ml; 7.1 mmol) were added. The reaction mixture was stirred for 7 hours under reflux. The isolation was carried out as in Example 6. After evaporation under reduced pressure, the product was optionally purified on a silica gel column using the system methylene chloride-methanol-conc. ammonia 90:9:1.5 to give the title product (1.11 g) with the following physico-chemical constants:

EI-MS m/z 688

TLC, chloroform-methanol-conc. ammonia, 60 : 10 : 1 Rf 0.667

methylene chloride-methanol-conc. ammonia, 90 : 9 : 1.5 Rf 0.415

(IR) (KBr) cm^{-1} 3457, 2974, 2937, 2788, 1717, 1456, 1382, 1331, 1258, 1185, 1163, 1109, 1078, 1050, 1005, 934, 871, 831, 755, 666.

^1H NMR (600 MHz, CDCl_3) δ 4.96 (H-13), 4.88 (H-1"), 4.21 (H-1'), 3.83 (H-11), 3.74 (H-5"), 3.72 (H-3), 3.48 (H-5'), 3.46 (H-3"), 3.41 (3"-OCH₃), 3.41 (H-5), 3.26 (H-10), 3.26 (H-2'), 3.15 (H-4"), 2.79 (H-8a), 2.79 (H-8b), 2.78 (H-2), 2.63 (H-7a), 2.55 (H-3'), 2.36 (H-2"a), 2.33 (3'-N(CH₃)₂), 1.88 (H-6), 1.84 (H-4), 1.77 (H-12), 1.71 (H-4'a),

1.53 (H-7b), 1.51 (H-2''b), 1.29 (5''-CH₃), 1.29 (13-CH₃), 1.27 (H-4'b), 1.23 (2-CH₃), 1.22 (5'-CH₃), 1.17 (4-CH₃), 1.15 (6-CH₃), 1.07 (12-CH₃), 1.06 (10-CH₃).

¹³C NMR (600 MHz, CDCl₃) δ 210.6 (C-9), 174.1 (C-1), 104.0 (C-1'), 99.8 (C-1''), 83.0 (C-5), 81.9 (C-3), 77.7 (C-3''), 75.7 (C-4''), 72.8 (C-13), 70.1 (C-2'), 69.4 (C-11), 68.9 (C-5'), 68.4 (C-5''), 65.1 (C-3'), 60.9 (C-8), 56.1 (3''-OCH₃), 51.1 (8-CH₂), 44.8 (C-2), 42.4 (C-10), 42.3 (C-4), 40.1 (C-12), 39.9 (3'-N(CH₃)₂), 33.9 (C-2''), 31.7 (C-7), 31.0 (C-6), 28.3 (C-4'), 20.8 (5'-CH₃), 19.2 (6-CH₃), 17.2 (5''-CH₃), 15.5 (13-CH₃), 14.5 (2-CH₃), 11.0 (12-CH₃), 9.6 (4-CH₃), 8.7 (10-CH₃).

Example 8

1-methoxy-1,13-seco-oleandomicyn-9,13-hemiketal (4C)

To a solution of 3'-N-demethyl-1-methoxy-1,13-seco-oleandomicyn-9,13-hemiketal (1.19 g; 1.7 mmol) from Example 5 in CHCl₃ (80 ml), 36% formaldehyde (0.274 ml; 9.9 mmol) and 98-100% formic acid (0.252 ml; 6.7 mmol) were added. The reaction mixture was stirred for 5 hours under reflux. The isolation was carried out as in Example 6. After evaporation under reduced pressure the product was optionally purified on a silica gel column using the system methylene chloride-methanol-conc. ammonia 90:9:1.5 to give the title product (0.85 g) with the following physico-chemical constants:

EI-MS m/z 704

TLC, chloroform-methanol-conc. ammonia, 60 : 10 : 1 R_f 0.759

methylene chloride-methanol-conc. ammonia, 90 : 9 : 1.5 R_f 0.509

(IR) (KBr) cm⁻¹ 3465, 2973, 2936, 2788, 1733, 1456, 1383, 1298, 1260, 1199, 1163, 1109, 1078, 1050, 1005, 987, 932, 895, 833, 755, 666.

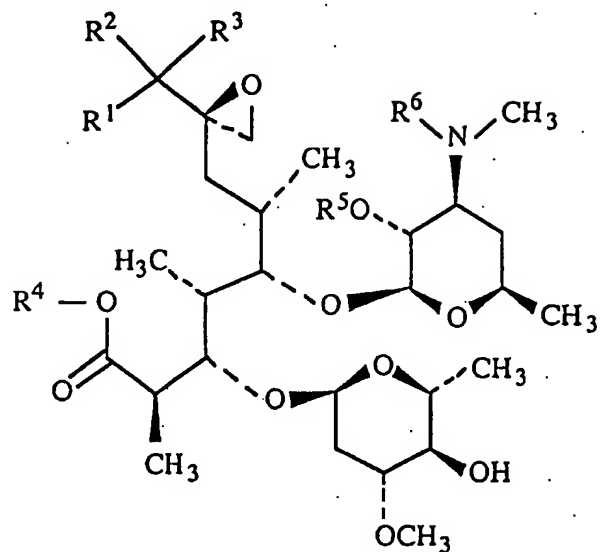
¹H NMR (500 MHz, CDCl₃) δ 4.88 (H-1''), 4.29 (H-1'), 4.15 (H-13), 4.00 (H-3), 3.78 (H-5''), 3.69 (1-OCH₃), 3.49 (H-5'), 3.45 (H-3''), 3.41 (H-5), 3.40 (3''-OCH₃), 3.27 (H-2'), 3.14 (H-4''), 2.83 (H-8a), 2.81 (H-2), 2.67 (H-8b), 2.52 (H-3'), 2.38 (H-7a), 2.30 (3'-N(CH₃)₂), 2.25 (H-2''a), 2.12 (H-10), 1.87 (H-6), 1.85 (H-4), 1.82 (H-11a), 1.67 (H-4'a), 1.62 (H-12), 1.47 (H-7b), 1.44 (H-2''b), 1.37 (H-11b), 1.28 (H-4'b), 1.28 (5''-

CH₃), 1.23 (5'-CH₃), 1.16 (2-CH₃), 1.11 (6-CH₃), 1.04 (4-CH₃), 1.04 (13-CH₃), 0.99 (12-CH₃), 0.81 (10-CH₃).

¹³C NMR (500 MHz, CDCl₃) δ 175.7 (C-1), 104.2 (C-1'), 98.1 (C-1''), 97.4 (C-9), 83.0 (C-5), 80.6 (C-3), 78.0 (C-3''), 75.8 (C-4''), 70.3 (C-2'), 69.0 (C-5'), 68.3 (C-5''), 66.9 (C-13), 65.2 (C-3'), 60.5 (C-8), 56.1 (3''-OCH₃), 51.6 (1-OCH₃), 49.6 (8-CH₂), 42.0 (C-2), 40.1 (3'-N(CH₃)₂), 38.9 (C-4), 35.6 (C-11), 34.0 (C-2''), 32.1 (C-12), 31.3 (C-6), 30.0 (C-7), 28.8 (C-4'), 27.3 (C-10), 21.0 (5'-CH₃), 18.3 (4-CH₃), 18.2 (13-CH₃), 17.4 (5''-CH₃), 15.9 (10-CH₃), 11.7 (12-CH₃), 11.5 (2-CH₃), 10.2 (6-CH₃).

CLAIMS

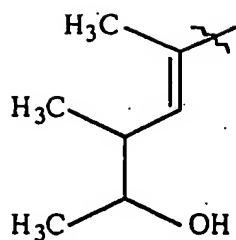
1. A compound of the general formula (I)



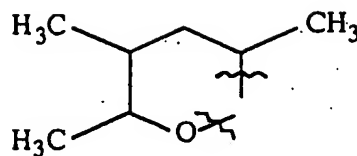
I

wherein

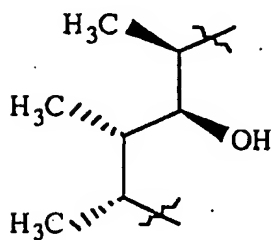
R¹ has the individual meaning of -CH₂CH₃ group, of a fragment of the formula (II), together with R² has the meaning of a fragment of the formula (III) or together with R⁴ has the meaning of a fragment of the formula (IV) or a fragment of the formula (V)



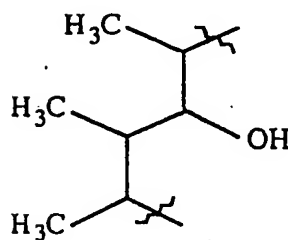
II



III



IV



V

R^2 together with R^3 has the meaning of a ketone or together with R^1 has the meaning of a fragment of the formula (III),

R^3 has the individual meaning of OH group or together with R^2 has the meaning of a ketone,

R^4 has the individual meaning of a methyl group, or together with R^1 has the meaning of a fragment of the formula (IV) or of a fragment of the formula (V),

R^5 has the individual meaning of hydrogen or a benzyloxycarbonyl group,

R^6 has the individual meaning of hydrogen, a methyl group or a benzyloxycarbonyl group,

and pharmaceutically acceptable addition salts thereof with inorganic or organic acids.

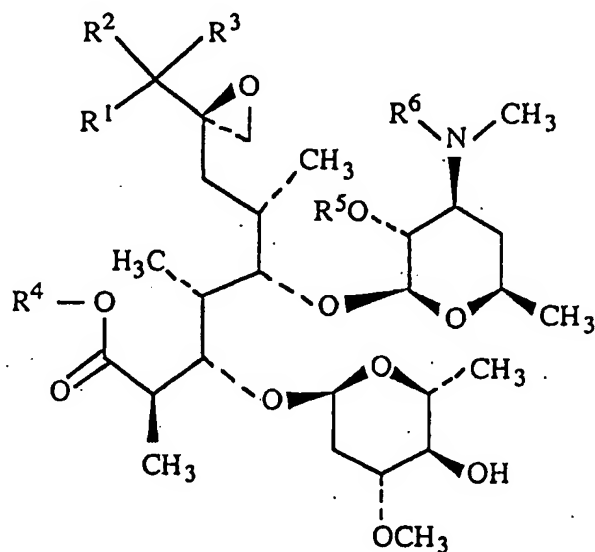
2. A compound according to claim 1, characterized in that R^1 together with R^4 has the meaning of a fragment of the formula (IV), R^2 together with R^3 has the meaning of a ketone and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group.

3. A compound according to claim 1, characterized in that R^1 has the meaning of $-CH_2CH_3$ group, R^2 together with R^3 has the meaning of a ketone, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group.
4. A compound according to claim 1, characterized in that R^1 together with R^4 has the meaning of a fragment of the formula (V), R^2 together with R^3 has the meaning of a ketone and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group.
5. A compound according to claim 1, characterized in that R^1 has the meaning of a fragment of the formula (II), R^2 together with R^3 has the meaning of a ketone, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group.
6. A compound according to claim 1, characterized in that R^1 has the meaning of $-CH_2CH_3$ group, R^2 together with R^3 has the meaning of a ketone, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of hydrogen.
7. A compound according to claim 1, characterized in that R^1 together with R^4 has the meaning of a fragment of the formula (V), R^2 together with R^3 has the meaning of a ketone and R^5 and R^6 are the same and have the meaning of hydrogen.
8. A compound according to claim 1, characterized in that R^1 together with R^2 has the meaning of a fragment of the formula (III), R^3 is an OH group, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of hydrogen.
9. A compound according to claim 1, characterized in that R^1 has the meaning of $-CH_2CH_3$ group, R^2 together with R^3 has the meaning of a ketone, R^4 and R^6 are the same and have the meaning of a methyl group and R^5 is hydrogen.

10. A compound according to claim 1, characterized in that R^1 together with R^4 has the meaning of a fragment of the formula (V), R^2 together with R^3 has the meaning of a ketone, R^5 is hydrogen and R^6 is a methyl group.

11. A compound according to claim 1, characterized in that R^1 together with R^2 has the meaning of a fragment of the formula (III), R^3 is an OH group, R^4 and R^6 are the same and have the meaning of a methyl group and R^5 is hydrogen.

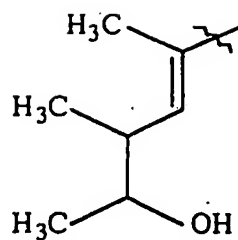
12. A process for preparing of a compound of the general formula (I)



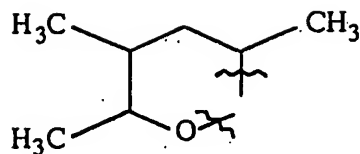
I

wherein

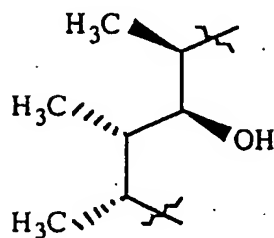
R^1 has the individual meaning of $-CH_2CH_3$ group, of a fragment of the formula (II), together with R^2 has the meaning of a fragment of the formula (III) or together with R^4 has the meaning of a fragment of the formula (IV) or a fragment of the formula (V)



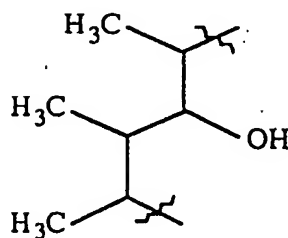
II



III



IV



V

R^2 together with R^3 has the meaning of a ketone or together with R^1 has the meaning of a fragment of the formula (III),

R^3 has the individual meaning of OH group or together with R^2 has the meaning of a ketone,

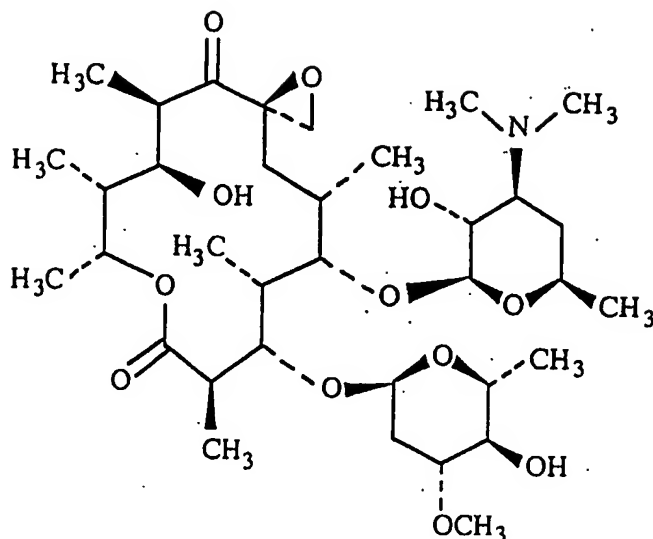
R^4 has the individual meaning of a methyl group, or together with R^1 has the meaning of a fragment of the formula (IV) or of a fragment of the formula (V),

R^5 has the individual meaning of hydrogen or a benzyloxycarbonyl group,

R^6 has the individual meaning of hydrogen, a methyl group or a benzyloxycarbonyl group,

and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, characterized in that

oleandomycin of the formula (VI)



VI

is subjected to a reaction with benzyloxycarbonyl chloride in the presence of a base, preferably sodium hydrogen carbonate, in a solvent inert in the reaction, preferably benzene or toluene, to obtain 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethyloleandomycin of the general formula (I), wherein R^1 together with R^4 has the meaning of a fragment of the formula (IV), R^2 together with R^3 has the meaning of a ketone and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group, which is then subjected to the action of a corresponding methylation agent, preferably methyl iodide, in the presence of a corresponding base, preferably sodium hydride, at a temperature from -15°C to room temperature, preferably at $0-5^\circ\text{C}$, in an appropriate aprotic solvent or solvent mixture, preferably DMSO-THF = 1:1, and to separation on a silica gel column in the system toluene-ethyl acetate = 1:1 to obtain a chromatographically homogenous compound **2A** of the general formula (I), wherein R^1 has the meaning of $-\text{CH}_2\text{CH}_3$ group, R^2 together with R^3 has the meaning of a ketone, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group,

a compound **2B** of the general formula (I), wherein R^1 together with R^4 has the meaning of a fragment of the formula (V), R^2 together with R^3 has the meaning of a

ketone and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group, and

a compound **2C** of the general formula (I), wherein R^1 has the meaning of a fragment of the formula (II), R^2 together with R^3 has the meaning of a ketone, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of a benzyloxycarbonyl group,

each of them is separately subjected to a hydrogenolysis reaction in a lower alcohol solution, preferably in ethanol, in the presence of NaOAc/HOAc buffer (pH 5) with a catalyst such as palladium black or palladium on carbon, under hydrogen pressure of 10^5 Pa at room temperature to obtain, respectively,

in case of **2A**, a compound **3A** of the general formula (I), wherein R^1 - R^4 have the meaning as given for the compound **2A** and R^5 and R^6 are the same and have the meaning of hydrogen, and

in case of **2B**, a compound **3B** of the general formula (I), wherein R^1 - R^4 have the meaning as given for the compound **2B** and R^5 and R^6 are the same and have the meaning of hydrogen, and

in case of **2C**, a compound **3C** of the general formula (I), wherein R^1 together with R^2 has the meaning of a fragment of the formula (III), R^3 is an OH group, R^4 is a methyl group and R^5 and R^6 are the same and have the meaning of hydrogen,

each of them is separately subjected to a reductive *N*-methylation in 3' position with 1-6.2 equivalents of formaldehyde (36%) in the presence of 1-4.2 equivalents of formic acid (98-100%) or some other hydrogen source, in a solvent inert in the reaction such as halogenated hydrocarbons, lower alcohols or lower ketones, preferably chloroform, at the reflux temperature of the reaction mixture, to obtain, respectively,

in case of **3A**, a compound **4A** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **2A**, R^5 is hydrogen and R^6 is a methyl group, and

in case of **3B**, a compound **4B** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **2B**, R^5 is hydrogen and R^6 is a methyl group, and

in case of **3C**, a compound **4C** of the general formula (I), wherein R^1 - R^4 have the meanings as given for the compound **3C**, R^5 is hydrogen and R^6 is a methyl group,

which are then optionally subjected to a reaction with inorganic or organic acids to obtain pharmaceutically acceptable addition salts thereof.